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Inhibition of allergen-induced wheal and flare reactions by levocetirizine and desloratadine

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The reproducible and standardized histamine-induced wheal and flare model helps identify the objective effectiveness of antihistamines in humans, as well as their differences in onset and duration of action.
- Some of the newest antihistamines have already been compared in a head-to-head setting using this model. However, their objective action at inhibiting the allergen-induced wheal and flare response has not been reported yet.

WHAT THIS STUDY ADDS

- The time–response study presented here shows the objective activity of two of the newest generation of antihistamines, levocetirizine and desloratadine, at inhibiting the allergen-induced wheal and flare response in a randomized, cross over, placebo-controlled trial.
- This model is interesting to the clinical setting since allergic subjects are recruited, and the response to allergen involves mast cell degranulation and release of numerous vasoactive and pro-inflammatory mediators additionally to histamine.
- In addition, this study reports receptor occupancy for both antihistamines at therapeutic dosage, leading to analysis of potential differences in activity.
- This study clearly shows the potential anti-inflammatory properties of desloratadine and levocetirizine in their skin activity when allergen is the challenging agent as occurs in the clinical situation.

AIMS

To evaluate the inhibitory activity of the new-generation antihistamines levocetirizine and desloratadine at their therapeutic doses on the allergen-induced wheal and flare reaction at 1.5 h, 4 h, 7 h, 12 h and 24 h postdose, and to measure their plasma and skin concentrations.

METHODS

A double-blind, randomized, cross-over, placebo-controlled study in 18 allergic subjects was carried out. The time–response of the wheal and flare reaction areas under the curve (AUC) were compared by ANOVA.

RESULTS

Both antihistamines significantly ($P < 0.001$) inhibited the allergen-induced wheal and flare reactions compared with placebo. Levocetirizine was significantly more potent than desloratadine. Mean ± SEM wheal AUC(0–24 h) was 506.4 ± 81.0 with levocetirizine and 995.5 ± 81.0 mm^2 h with desloratadine as compared with placebo (1318.5 ± 361.0 mm^2 h). Flare AUC(0–24 h) was 5927.3 ± 1686.5 and 15 838.2 ± 1686.5 mm^2 h, respectively [$P < 0.001$ for both compared with placebo (22508.2 ± 7437.1 mm^2 h)]. Levocetirizine showed significant inhibition of wheal and flare already at 1.5 h postdose compared with placebo ($P \leq 0.001$); desloratadine achieved a significant effect only after 4 h. The mean total plasma concentration at 12 h and 24 h after intake was higher for levocetirizine (58.1 ± 13.4 and 20.0 ± 8.1 ng ml^{-1}, respectively) as compared with desloratadine (0.82 ± 0.24 and 0.45 ± 0.16 ng ml^{-1}). Similarly, higher mean unbound skin concentrations were observed for levocetirizine 24 h after intake (1.80 ng g^{-1}) than for desloratadine (0.07 ng g^{-1}). This was associated with greater receptor occupancy for levocetirizine (54%) than desloratadine (34%) at 24 h.

CONCLUSIONS

Levocetirizine suppressed the cutaneous allergic reactions with a higher potency than desloratadine, which correlated with its high receptor occupancy. Receptor occupancy rather than drug affinity or plasma half-life is more representative of antihistamine potency.

Introduction

The prevalence of allergic diseases has increased considerably over the last several decades [1] as have the treatment options. Antihistamines are the first line treatment for most of the upper airway and skin allergic conditions. The existence of several generations of antihistamines and of many products within each generation sometimes makes it difficult for physicians to choose the best possible treatment option for their patients. This is partly due to the fact that the differences between the available antihistamines in routine clinical practice are not readily discernible and that sufficient comparative data are not available from controlled clinical trials. Fortunately, precision challenge studies can be employed to help identify these differences and consequently help clinical decision making. Their advantages over traditional clinical studies are that they are reproducible, allow reliable comparisons due to their standardized procedure, are usually more sensitive, and allow assessment of onset and duration of drug activity [2].

Histamine is one of the major known mediators of allergic inflammatory reactions and has traditionally been used as a challenge in skin pharmacodynamic studies of the antihistaminic activity of new compounds. However, the validity of the histamine-induced wheal and flare model to predict clinical efficacy may be strengthened by studies using challenge with the specific allergens against which the subject is sensitized, as normally used for the diagnosis of allergy by skin prick testing. An advantage is that allergen-induced wheal and flare studies recruit allergic subjects rather than healthy volunteers. This model is closer to the clinical setting when compared with the recruitment of nonsensitized healthy subjects in histamine-induced wheal and flare models. Such advantages make allergen-induced wheal and flare studies more relevant to clinical problems and valuable for practicing physicians.

Comparative studies using histamine-induced models [3, 4] have reported higher potency for levocetirizine compared with desloratadine over a 24 h study period, although such results do not fit well with the higher receptor affinity [5] established *in vitro*, the longer dissociation half-time from the H_1-receptors [6], and the longer plasma elimination half-life [7] reported *in vivo* for desloratadine. Therefore, in addition to their potency in inhibiting the allergen-induced skin wheal and flare reactions, we were also interested in evaluating the plasma and skin concentrations of the study drugs in order to calculate their receptor occupancy.

Levocetirizine and desloratadine are considered to be improvements over their parent molecules. Levocetirizine is the active R-enantiomer of cetirizine [8] and desloratadine is the active metabolite of loratadine [9]. The aim of this study was to compare the inhibitory activity of levocetirizine 5 mg and desloratadine 5 mg on allergen-induced wheal and flare reactions over a period of 24 h, after a single intake of the study drugs in 18 allergic subjects, and to investigate whether their receptor occupancy, 24 h after drug intake, could help to explain their pharmacodynamic potency.

Methods

This was a prospective, randomized, double-blind, placebo-controlled, three-way crossover study conducted in 18 allergic subjects recruited in one centre. There were three single dose treatment periods per subject (visits 2–4) with a wash-out period of 14–21 days between treatments. The screening visit took place 14–21 days prior to the first study drug administration and subjects completed the study within 7 days after the last treatment period. Subjects received one tablet of each of the study medications (levocetirizine 5 mg, desloratadine 5 mg and placebo) in a randomized order. Study medications were taken in the morning (between 07.00 h and 09.00 h) on day 1 of each treatment period after the predose skin prick tests (time 0).

At the screening visit, subjects aged 18–50 years and with an established history of allergy were required to sign an informed consent form, which was approved by the hospital ethics committee. Subjects were also required to fulfil at least the following major inclusion criteria: positive skin prick tests and a positive radio-allergosorbent test (RAST) of ≥class 2 for one of the most common allergens: grass and tree pollens, house dust mites, cat and dog dander; absence of allergic symptoms for at least 1 month before and during the study; a negative pregnancy test and the use of a medically accepted contraceptive method for female subjects; good physical and mental health status (as per medical history and general clinical examination); normal laboratory results. Subjects were excluded if they had any concomitant chronic or acute illness; if they had a history of or current cardiovascular (including cardiac arrhythmias), respiratory, hepatic, renal, gastrointestinal, endocrinological, neurological, or psychiatric disease; anaphylactic shock as well as disorders capable of altering the absorption, metabolism or elimination of drugs, or constituting a risk factor when taking the trial medication. Heavy caffeine drinkers (>five cups of coffee, tea, cola, etc. per day) were also excluded. Subjects were required to have no known allergy or intolerance to the study drugs, to drugs related to the study procedures, as well as any medicine chemically related to the study drugs or their excipients. Any drug treatment except hormonal contraceptives or postmenopausal hormone replacement therapy for females and occasional use of paracetamol not exceeding 2 g day^{-1} with a maximum dose of 10 g 14 $days^{-1}$ had to be discontinued at least 14 days before study drug administration (at least 4 weeks for systemic corticosteroids). Subjects who received immunotherapy and those with exposure to skin irritants or UV light in the 48 h before each visit were also excluded.

Subjects were free to withdraw from the study at any time and for any reason. The investigator could also withdraw a subject for reasons of safety or protocol deviation that could invalidate the interpretation of the results.

As all investigational products were not of the same shape, size and colour, they were administered in a third-party blinded manner where tablets placed in a blinded, sealed container, were put in the open mouth of a subject by an experienced staff member who was not involved in the study procedures. Neither the subjects nor the team performing the skin tests and tracing the wheal and flare saw the tablets/blisters before, during or after administration in each study period.

Study procedures

The specific allergen and its specific concentration to be used for each subject were determined by a skin prick test during the screening visit, where the positive allergen extract was studied at three increasing concentrations (1, 10 and 100 IR). The allergen concentration leading to the greatest wheal reaction was selected. The allergen skin prick test was considered positive if the wheal area was >75% of the wheal area induced by the positive control, i.e. histamine hydrochloride 10 mg ml^{-1}. Skin prick tests (Prick Lancet, Stallergènes, France) were performed with the same batch of standardized extracts and at the same concentration for each prick test in each subject throughout the study. The allergen drop was wiped off with an absorbent paper 1 min after the skin prick. The tests were carried out in duplicate by the same investigator on the left and right forearms, and at the same place between treatment periods in each subject. Six allergen skin prick tests were performed, successively, on each forearm at predose, 1.5, 4, 7, 12 and 24 h postdose. Fifteen minutes after each skin prick test, the wheal and flare reactions were outlined and transferred to a rubber tape glued on a transparent paper. They were then scanned using Photoshop® software and analyzed with the public domain NIH Image program. Results were expressed in mm^2 and presented as the mean of both measurements observed on the left and the right forearms.

Plasma samples were obtained at three time points: before treatment, 12 and 24 h after drug intake. Samples of 10 ml were collected by venipuncture of the forearm in empty tubes containing lithium heparin and kept at +4°C. The blood was centrifuged at +4°C within 30 min after sampling at approximately 1500 *g* for 15 min. The resulting plasma was frozen in two separate polypropylene tubes at −20°C or below until shipment to the bio-analytical laboratory after the last treatment period.

Skin biopsies were performed on the internal surface of the forearm using a 3 mm Accu Punch® device, 24 h postdose. A local anaesthetic was used. All biopsy samples were blotted free of blood using surgical gauze, transferred to a nonabsorbent paper, stored in a sealed and labelled polypropylene tube, and frozen upright at −20°C or below until shipping.

All compounds and the respective internal standards were analyzed after sample extraction by liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) in the Turbo Ion Spray positive mode. The LC-MS/MS method for the analysis of levocetirizine and desloratadine in human plasma with a lower limit of quantification (LLOQ) of 0.2 ng ml^{-1} and 0.1 ng ml^{-1}, respectively, has been previously developed and fully validated by PAREXEL International Bioanalytical Laboratories (Poitiers, France). The method was adapted also for the analysis of the two compounds in skin biopsy samples with a LLOQ of 25 ng g^{-1} for both drugs. A standard plasma curve was performed every day of analysis between 0.2 and 500 ng ml^{-1} for levocetirizine and between 0.1 and 20 ng ml^{-1} for desloratadine. The concentrations of both drugs were calculated as ng ml^{-1} in human plasma and as ng g^{-1} in skin biopsy samples. The concentration assessments were conducted in accordance with good laboratory practice regulation of the Organization for Economic Cooperation and Development.

Primary parameters

The primary parameters were the areas under the curve of the allergen-induced wheal and flare areas for each treatment from 0 to 24 h (AUC(0–24 h)), calculated by the trapezoidal rule.

Secondary parameters

The following secondary parameters for each treatment group were also evaluated: the wheal and flare areas at each time point; the mean AUC(0–12 h); the wheal and flare area inhibition (%) from baseline using the formula:

$$W/F\ inh(t) = 100 \times (W/F0 - W/Ft)/W/F0$$

where Wt and Ft were the wheal and flare area, respectively, at time point *t*; the maximal wheal and flare inhibition (%) observed at any time; the proportion of subjects with a wheal or flare inhibition of at least 50%; the total plasma drug concentrations (*C*p); the total skin concentrations (*C*s); the unbound skin concentrations using the formula:

$$Cs \times FUS$$

where FUS is the unbound skin fraction calculated with the formula:

$$FUS = (FUP \times Cp)/Cs$$

(FUP is the unbound fraction in plasma: 0.09 for levocetirizine [10] and 0.15 for desloratadine [11]); the receptor occupancy using the formula from Gillard *et al.* [12]:

$$RO\ percentage = B_{max}(100\%) \times L/(L + K_i)$$

where L is the free concentration of the drug at the active site (histamine H_1 receptor), B_{max} is the maximal number of

binding sites (set to 100%) and K_i is the equilibrium inhibition constant; the general safety and tolerability of each treatment assessed through adverse events (AEs), vital signs, physical examination and laboratory results.

Statistical analysis

The primary variables were analyzed using analysis of variance (ANOVA) for cross-over design including the following fixed effects: period, sequence and treatment. Subjects' effect, nested within sequence, was considered as a random effect. The treatment effect was estimated by calculating the difference in least squares means for each pair-wise comparison (the one between levocetirizine and desloratadine being of primary interest) and its associated 95% confidence interval.

Results

Patients

Eighteen subjects (nine females) were screened, randomized and completed the study. No subject was excluded from study analysis. All subjects were Caucasian and aged between 18.5 and 48.1 years. The mean weight and height were 66.2 kg (ranging from 54 to 93 kg) and 170.5 cm (ranging from 158 to 186 cm), respectively. All subjects suffered from an allergy (either seasonal, allergy to house dust mites or to animal dander). There was a positive skin prick test for grass pollens in 16 subjects (88.9%), for tree pollens in eight subjects (44.4%), for cat dander in six subjects (33.3%) and for house dust mites in five subjects (27.8%). No positive result was observed with dog dander. The number of subjects with a positive RAST (≥2) was 15 (83.3%) for grass pollens, eight (44.4%) for birch pollens, seven (38.9%) for house dust mites and five (27.8%) for cat dander. The specific allergen selected for use during the treatment period was grass pollen for 13 subjects (72.2%), tree pollen for three subjects (16.7%) and house dust mites for two subjects (11.1%).

Pharmacodynamics of anti-H_1 compounds

Analysis of the AUC(0–24 h) showed that the cutaneous reactivity to allergen (both wheals and flares) was significantly inhibited by both the active medications ($P < 0.001$ for both drugs *vs.* placebo). Also, levocetirizine was significantly more potent in inhibiting the reactions to allergen than desloratadine ($P < 0.001$ for both wheal and flare areas; Figure 1a, b).

The results of the AUC over the first 12 h (AUC(0–12 h)) for wheal and flare reactions were similar to those of the whole 24 h period [AUC(0–24 h)]. Levocetirizine was significantly more potent in inhibiting the cutaneous reactions during the first 12 h than desloratadine ($P < 0.001$ for both wheal and flare areas).

Over time, from 1.5 h to 24 h postdose, the largest mean wheal and flare areas were observed after placebo (Figure 2a, b). At any time point, the smallest mean wheal and flare areas were measured with levocetirizine. The desloratadine curves were always situated between the other two. For wheal and flare areas, the three curves never crossed.

The mean inhibition (%) of the wheal and flare areas was already significant with levocetirizine at 1.5 h after drug intake (37% for wheal and 34% for flare). Both

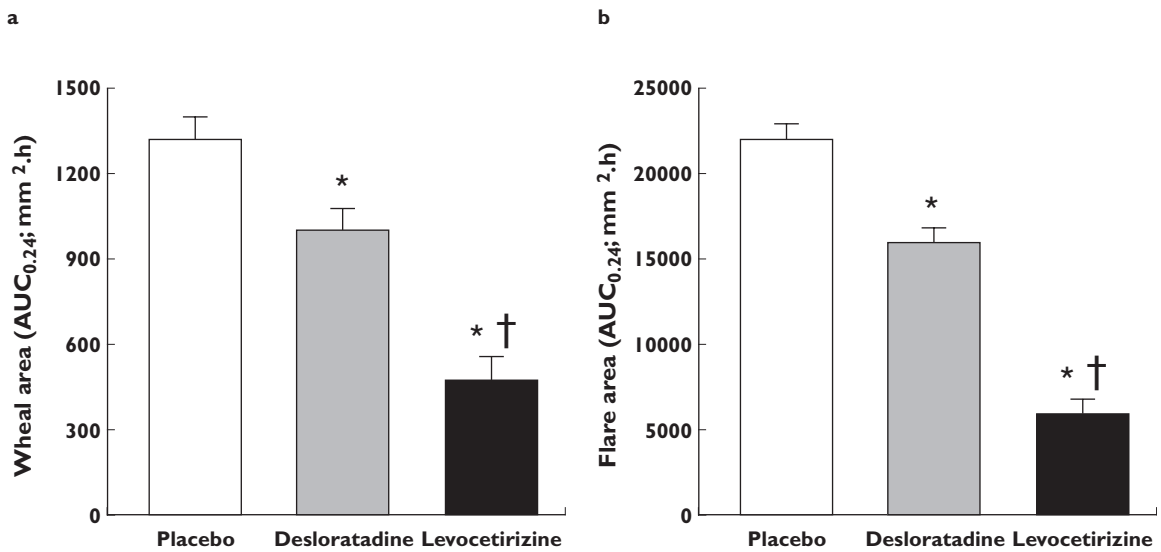

Figure 1

AUC(0–24 h) of wheal (a) and flare (b) areas. Blocks are means and bars are SEM of results in $n = 18$ subjects per group. *$P < 0.001$ *vs.* placebo, †$P < 0.001$ *vs.* desloratadine

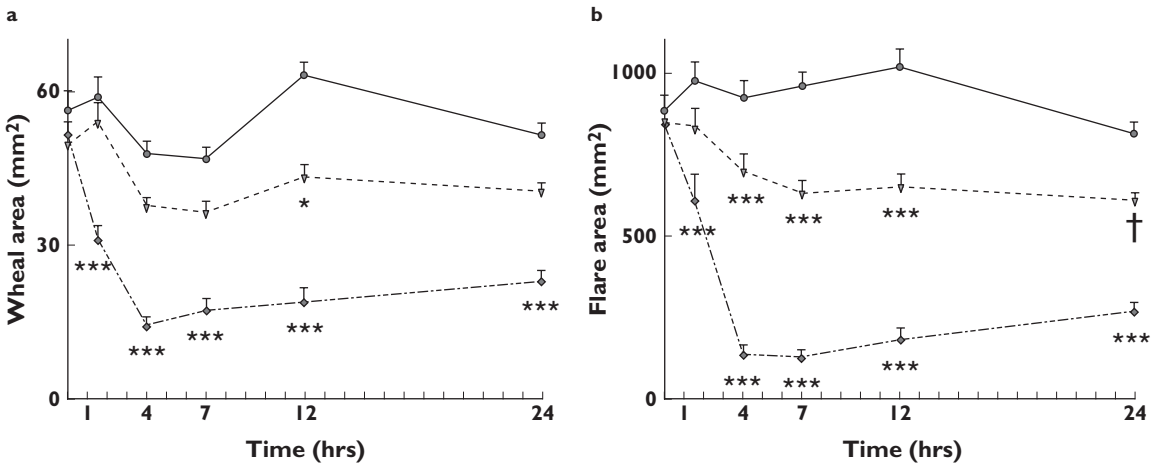

Figure 2

Areas (mm^2) of wheal (a) and flare (b) during the 24 h after drug intake. Points are means and bars are SEM of areas obtained in $n = 18$ subjects per group. ***$P \leq 0.0001$ (for levocetirizine *vs.* placebo and *vs.* desloratadine; and for desloratadine *vs.* placebo); *$P < 0.01$ (*vs.* placebo), †$P = 0.0003$ (*vs.* placebo). Placebo, (●); Desloratadine 5 mg, (▽); Levocetirizine 5 mg, (◆)

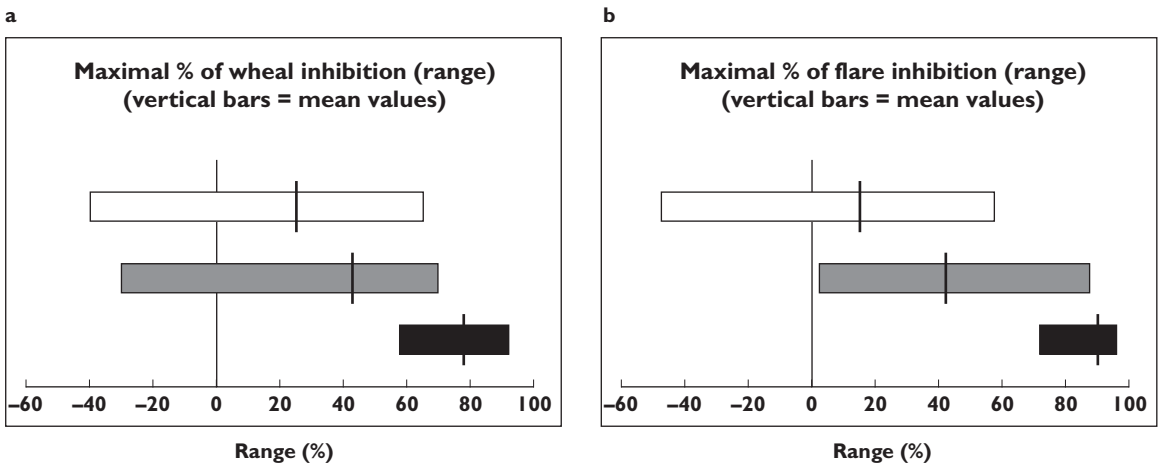

Figure 3

Ranges of the maximal wheal (a) and flare (b) inhibition (%) in $n = 18$ volunteers per group at any time point. Placebo, (□); Desloratadine 5 mg, (▩); Levocetirizine 5 mg, (■)

placebo and desloratadine were not yet active at that early measurement time point.

The maximal inhibition with placebo was 11% for wheal, occurring at the 7th hour postdose, and 6% for flare, at the 24th hour postdose. Maximal inhibitions were higher for desloratadine: 23% at the 7th hour postdose for wheal and 33% at the 24th hour postdose for flare. These were highest with levocetirizine: 72% at the 4th hour postdose for wheal and 87% at the 7th hour postdose for flare areas.

The ranges of the maximal percentage of wheal or flare inhibition per treatment recorded at any time point are presented in Figure 3.

Although the greatest individual percentage of wheal or flare inhibitions with placebo reached >50% at certain time points for some volunteers (Figure 4), the proportion of subjects with at least 50% inhibition remained very low. In contrast, when taking levocetirizine, a greater number of subjects (>80%) had allergen-induced wheal (Figure 4a) or flare (Figure 4b) inhibition at all time points compared with desloratadine.

Plasma and skin drug concentrations

The total plasma concentrations of levocetirizine and desloratadine before their intake were, as expected not quantifiable. The mean total plasma concentration of levo-

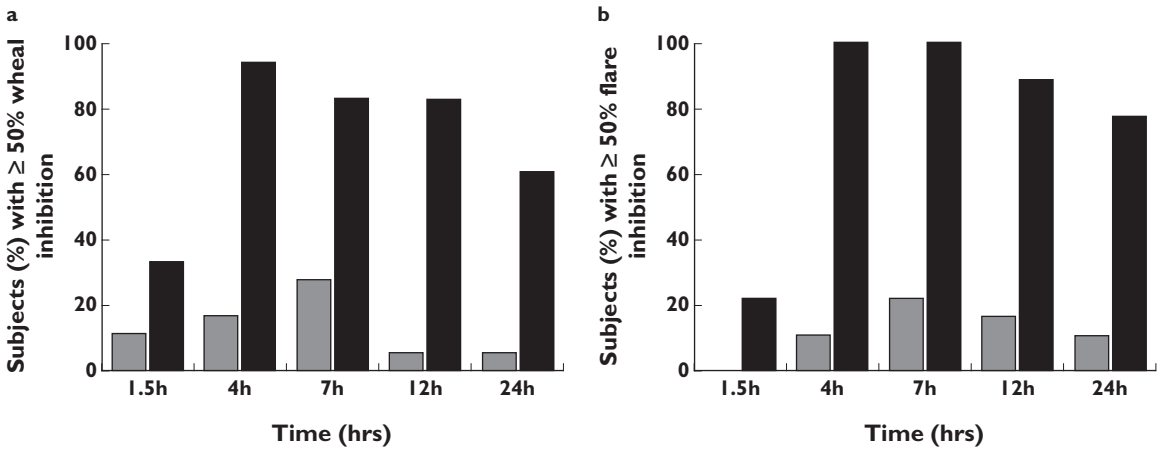

Figure 4

Frequency of subjects achieving ≥50% inhibition of the wheal (a) and flare (b) areas over a 24 h period after drug intake. Placebo results are not included since percentages of inhibition remained very low or negative ($n = 18$ subjects per group). Desloratadine 5 mg, (▩); Levocetirizine 5 mg, (■)

Table 1

Drug concentrations, receptor occupancy parameters, and wheal and flare inhibition, measured 24 h after drug intake. Results are means (SEM) obtained from 18 patients

Parameter	Desloratadine 5 mg ($n = 18$)	Levocetirizine 5 mg ($n = 18$)
Total plasma concentration (ng ml^{-1})	0.45 (0.16)	20.03 (8.13)
Total skin concentration (ng g^{-1})	56.33 (55.06)	40.73 (18.99)
Unbound fraction in skin (%)	0.002 (0.001)	0.048 (0.01)
Unbound skin concentration (ng g^{-1})	0.07 (0.02)	1.80 (0.73)
Receptor occupancy (%)	34	54
Wheal inhibition *vs.* placebo (%)	22	54
Flare inhibition *vs.* placebo (%)	26	66

cetirizine at 12 h after intake was 58.14 ± 13.41 ng ml^{-1} and that of desloratadine was 0.82 ± 0.24 ng ml^{-1}. Detailed values for total plasma and skin concentrations as well as unbound skin concentrations and receptor occupancy at 24 h are presented in Table 1. Although the total skin concentration was higher for desloratadine than levocetirizine, the unbound fraction in skin, as well as the unbound skin concentration and the corresponding receptor occupancy were lower for desloratadine than levocetirizine.

Safety results

During the study, 12 treatment-emergent adverse events were reported by the subjects. Four subjects (22.2%) reported at least one AE with placebo, one subject (5.6%) with levocetirizine and four subjects (22.2%) with desloratadine. Two placebo subjects and two desloratadine subjects reported at least one AE that was considered by the investigator as drug-related. The intensity of reported AEs was mild or moderate with no severe AEs. No subject discontinued the study due to an AE.

Discussion

The wheal and flare reaction in response to allergen is a very common technique routinely used by allergists to determine the sensitizing agent in allergic patients. These patients frequently take antihistamines, either on prescription or as self-medication, and if an appropriate wash-out period between the drug discontinuation and the test is not observed, the outcome can provide false negative results. We have previously used this technique to establish the wash-out period necessary after ebastine intake [13]. Here we report the results of the inhibitory activity of two recently introduced antihistamines, levocetirizine and desloratadine, on the allergen-induced wheal and flare response over a 24 h period, including their onset and duration of action.

The results of this study largely confirm and extend the results of previously reported wheal and flare studies, which employed histamine as the challenging agent. We have used here a challenge to the specific allergen to which the subjects were sensitized, allowing the assess-

ment of the antiallergic activity of levocetirizine and desloratadine in addition to their antihistaminic potency. A cross-over design was chosen in order to minimize the variability by ensuring a within-subject treatment comparison. A 2 week wash-out period was considered sufficient to prevent any carry-over effects. Although multiple dosing is closer to clinical reality, we chose a single-dose intake since this is typically used in wheal and flare studies and also because 'on-demand' intake of antihistamines is a common clinical practice. The time–response design allowed us to compare not only the overall relative activity of the study drugs, but also to assess their onset and duration of action.

This study shows that both antihistamines were significantly more potent than placebo at inhibiting the cutaneous response to allergen similar to results obtained in previous histamine-induced wheal and flare studies [4, 14]. The areas under the curves of the wheal and flare areas over 12 or 24 h were significantly smaller with the two active medications when compared with placebo. This confirms the activity of levocetirizine and desloratadine in skin, and the appropriateness of using them once daily. There were, additionally, significant differences between the study antihistamines in their overall inhibitory activity. Levocetirizine showed a marked inhibitory activity on both wheal and flare by 1.5 h after intake whereas at the same time point desloratadine was not different either from placebo or from its own baseline. In addition, during its maximal inhibitory activity between 4 and 12 h after intake, the wheal and flare areas with desloratadine were significantly less inhibited than with levocetirizine.

Previous cutaneous histamine-induced studies have reported an almost total wheal and flare inhibition with levocetirizine. The wheals and flares induced by allergen in the present study were not totally inhibited by either study antihistamine, probably reflecting the more complex inflammatory process induced by mast cell mediators released upon allergen challenge. Despite this difference, the antihistaminic activity visualized by the time–response curves of wheal and flare areas, reflecting a clear difference in potency between the two antihistamines in our allergen challenge study, were very close to the ones reported in studies using histamine as the challenging agent [3]. This is important since the allergen-induced wheal and flare response involves some inflammatory components, which are likely to be inhibited by antihistamines. This therefore corroborates previous findings of the anti-inflammatory properties of levocetirizine [15–17] and desloratadine [18–20].

Overall, 30% of the subjects for wheal and 20% for flare only reached the 50% inhibition threshold when taking desloratadine, whereas the 18 out of 18 subjects (100%) taking levocetirizine had a 50% or more inhibition. Additionally, the ranges of maximal wheal inhibition over time were wider in the desloratadine treatment period for both wheal and flare areas as compared with levocetirizine. There were subjects who responded very well to desloratadine with maximal inhibitions reaching 70% for wheal and 87% for flare. However, there were also subjects whose maximal inhibitions were negative (wheal) or unchanged (flare), indicating inconsistency of the activity of desloratadine between subjects. By contrast, the effect of levocetirizine was consistent within subjects, with inhibitions always above 55% for wheal and 74% for flare. This confirms the previously reported results of the good consistency of activity of levocetirizine and the less consistent action of desloratadine at antagonizing the effect of cutaneous histamine [3]. This is of importance to the allergist clinician since it indicates that most, if not all, of the patients are likely to have relief of symptoms when taking levocetirizine.

A previous allergen-induced wheal and flare study comparing the parent molecules cetirizine and loratadine reported similar inhibitory activity for these two medications [21]. Taking the differences in the study designs into consideration, the fact that levocetirizine is significantly better than desloratadine in our study while cetirizine was not better than loratadine in the study by Persi *et al.* [21] suggests that the parent molecules and their derivatives have different absorption or biodistribution characteristics. This is what we planned to implement by studying the pharmacokinetics of both anti-H_1-receptor drugs at 12 and 24 h.

Although both drugs were administered at the same dose of 5 mg once daily, and in the same subjects in a cross-over design, the plasma concentrations of levocetirizine 12 and 24 h after intake were, respectively, 70 and 45 times higher than those of desloratadine. More importantly, despite the much higher total skin concentration of desloratadine, the unbound skin concentration, which can be approximated to the concentrations available at the receptor sites, i.e. the active concentrations at membrane receptors, was 23 times higher for levocetirizine than for desloratadine. Indeed, since the H_1-receptors are localized at the cellular membrane [22], an H_1-antihistamine does not need to be distributed inside the cells to be effective. As a consequence, the receptor occupancy for levocetirizine was higher than that of desloratadine. Therefore, the relatively low availability of desloratadine at the H_1-receptor sites could be a plausible explanation for its lower cutaneous antihistamine activity. Thus, the longer plasma elimination half-life of desloratadine [7] and its higher *in vitro* H_1-receptor affinity [5], do not translate into a more potent or longer duration of action compared with levocetirizine, probably due to the relatively low maximal concentration achieved in the extracellular space. Our results suggest that the relatively high concentrations of levocetirizine at the receptor sites, even 24 h after intake, are primarily responsible for the potency and long-lasting activity of the drug.

In conclusion, our allergen-induced wheal and flare study confirms the results from histamine-challenge

studies of a more potent activity of levocetirizine over that of desloratadine in skin. The higher potency of levocetirizine in suppressing the allergen-induced skin reactions relates well to the higher receptor occupancy of levocetirizine compared with desloratadine, therefore providing a plausible explanation for the superior cutaneous H_1-antihistamine activity of levocetirizine 5 mg over desloratadine 5 mg. Our results suggest that receptor occupancy, rather than drug affinity or plasma half-life, is more representative of the antihistamine activity. The results of this study will be useful to the allergist who needs to prescribe a potent, consistent and long-lasting medication for the treatment of urticaria.

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